ETHICAL ISSUES AND VACCINES

Biological Weapons, Bioterrorism, and Vaccines

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A biological attack by terrorists or a national power may seem more like a plot element in an action film than a realistic threat. And indeed, the possibility of such an attack may be very remote. Biological attacks, however, have occurred in the past, one as recently as 2001. Accordingly, a collection of U.S. government agencies are involved in planning responses to potential biological attacks.

Bio-weapon threats could include the deliberate release by attackers of an agent that causes one or more of various diseases. Public health authorities have developed a system to prioritize biological agents according to their risk to national security. Category A agents are the highest priority, and these are disease agents that pose a risk to national security because they can be transmitted from person to person, lead to high mortality, and/or have a high potential to cause social disruption. These are anthrax, botulism (via botulinum toxin, which is not passable from person to person), plague, smallpox, tularemia, and a collection of viruses that cause hemorrhagic fevers, such as Ebola, Marburg, Lassa, and Machupo. These disease agents exist in nature (except for smallpox, which has been eradicated in the wild), but they could be manipulated to make them more dangerous.

Category B agents are moderately easy to disseminate and result in low mortality. These include brucellosis, glanders, Q fever, ricin toxin, typhus fever, and other agents. Category C agents include emerging disease agents that could be engineered for mass dissemination in the future, such as Nipah virus. (This **index of possible threats** from the CDC lists all Category A, B, and C agents. Note that chemical weapons, such as those involving nonbiological substances such as chlorine gas, are not included.)

Effective vaccines would likely protect lives and limit disease spread in a biological weapons emergency. Licensed vaccines are currently available for a few threats, such as anthrax and smallpox, and research is underway to develop and produce vaccines for other threats, such as tularemia, Ebola virus, and Marburg virus. Many bio-weapon disease threats, however, lack a corresponding vaccine, and for those that do, significant challenges exist to their successful use in an emergency.

What Is a Bioterror Threat?

The draft Model State Emergency Health Powers Act of 2001, which is a document designed to guide legislative bodies as they draft laws regarding public health emergencies, has defined bio-terrorism as "the intentional use of any microorganism, virus, infectious substance, or biological product that may be engineered due to biotechnology, or any naturally occurring or bioengineered component of any such microorganism, virus, infectious substance, or biological product, to cause death, disease, or other biological malfunction in a human, an animal, a plant, or another living organism in order to influence the conduct of government or to intimidate or coerce a civilian population." Biological warfare and bio-terrorism are often used interchangeably, but bio-terrorism usually refers to acts committed by a sub-national entity, rather than a country.

How Likely Is a Biological Attack to Happen?

Expert opinions differ on the plausibility of a biological attack. The U.S. Office of the Director of National Intelligence and the National Intelligence Council stated in 2008 that bio-terrorism is more likely than nuclear terrorism. That same year, U.S. Director of National Intelligence Mike McConnell revealed that, of all weapons of mass destruction, biological weapons were his personal greatest worry (McConnell, 2008). Other defense experts and scientists insist that the possibility of any attack, especially a large-scale one, is small, given the immense challenges to cultivating, weaponizing, and deploying biological agents. For example, the technical difficulties in aerosolizing a disease agent and dispersing it accurately and widely while maintaining its virulence are immense. Regardless, most bio-security experts acknowledge that the potential of an attack should not be ignored. Moreover, preparations for a biological attack will likely benefit the response to other kinds of public health emergencies.

History of Biological Weapons

Biological weapons are not just a 21st century concern: humans have used infectious agents in conflicts for hundreds of years. Below are a few examples.

- In a 1336 attempt to infect besieged city dwellers, Mongol attackers in what is now the Ukraine used catapults to hurl the bodies of bubonic plague victims over the city walls of Caffa.
- Tunisian forces used plague-tainted clothing as a weapon in the 1785 siege of La Calle.
- British officers discussed plans to intentionally transmit smallpox to Native Americans during Pontiac's Rebellion near Fort Pitt (present-day Pittsburgh, Pennsylvania) in 1763. It is unclear whether they carried out these plans. But, whatever its source, smallpox spread among Native Americans in the area during and after that rebellion.
- The Japanese used plague as a biological weapon during the Sino-Japanese War in the late 1930s and 1940s. They filled bombs with plague-infected fleas and dropped them from airplanes onto two Chinese cities. They also used cholera and shigella as weapons in other attacks. An estimated 580,000 Chinese died because of the Japanese bio-weapons program (Martin et al., 2007).

The U.S. military developed biological weapons and investigated their effects in the 20th century. The U.S. Army's Biological Warfare Laboratories were based at Camp (later Fort) Detrick, Maryland, from 1949 to 1969. The program produced and weaponized several biological agents, including anthrax and botulinum toxin, though the biological weapons were never used in conflicts. President Richard Nixon ended the biological weapons program in 1969, and U.S. biological weapons were destroyed. U.S. research into biological weapons since that time has focused on defensive measures, such as immunization and response.

In 1975, the Biological and Toxin Weapons Convention (BTWC) came into force. More than 100 nations, including the United States, have ratified this international treaty, which aims to end the development and production of bio-weapons. Despite the agreement, bio-weapon threats from fringe groups, terrorists, and nations not committed to or observing the convention continue to worry public health authorities.

The former Soviet Union is known to have produced copious quantities of smallpox virus and many other disease agents in its bio-weapons program long after it signed the BTWC. In the 1970s, it stockpiled tons of smallpox virus and maintained production capability at least until 1990. The Soviet Union also sponsored an anthrax weapon program; an accidental release of a small amount of weaponized anthrax from a military research facility in 1979 led to at least 70 deaths. The U.S.S.R. claimed it destroyed its bio-weapons stock and dismantled the bio-weapons program in the late 1980s, but most experts are skeptical that all stocks, equipment, and records were destroyed. They regard it as possible that illicit transfer of biological materials or knowledge has occurred. So, while only two known sources of smallpox virus exist, both in World Health Organization reference laboratories, many suspect that other groups—whether national or subnational—may have unknown quantities of smallpox virus, as well as other remnants of the Soviet biological weapons program.

On a similar note, Iraq admitted to United Nations inspectors in the 1990s that it had produced thousands of tons of concentrated botulinum toxin and developed bombs to deploy large quantities of botulinum toxin and anthrax. Though the Iraqi government abandoned its bio-weapons program after the first Iraq war, the status and whereabouts of the large quantities of infectious material they developed are unknown.

Other groups of current concern for biosecurity experts include Al Qaeda, which had a large-scale bio-weapons effort in Afghanistan. This was destroyed when the U.S. bombed its facilities and training camps in 2001. Al Qaeda's program today is likely to be much smaller, because so much of its material and intellectual capital was destroyed. Most experts think Al Qaeda's current attempts to reconstitute the weapons are focused on chemical weapons, not biological ones. At a national level, a 2007 U.S. military assessment of biological threats included the following overview of bio-weapons programs: "According to an unclassified U.S. Department of State report in 2005, nations suspected of continued offensive biological warfare programs in violation of the BWC [Biological Weapons Convention] include China, Iran, North Korea, Russia, Syria, and possibly Cuba" (Martin et al., 2007).

Contemporary U.S. Attacks

Oregon followers of Indian guru Bhagwan Shree Rajneesh mounted an attack that sickened nearly 800 people with typhoid fever in 1984. Cult members introduced bacteria into salad bars and other restaurant food receptacles after their attempts to contaminate the local water supply failed. They hoped to influence local election results by preventing residents from voting. Though 43 people were hospitalized, no one was killed, and the wrongdoers were prosecuted.

A more recent U.S. biological attack occurred just after the Al Qaeda attacks of September 11, 2001, on the World Trade Center and the Pentagon. An unknown actor mailed a powder containing infectious anthrax spores to two U.S. senators and several media outlets. Five people died from anthrax after exposure to the material in the letters, and 17 became ill. Medical personnel offered the anthrax vaccine as post-exposure prophylaxis (PEP) to 1,727 potentially exposed people who were also taking antibiotics to counter anthrax. Of those people, 199 agreed to take the vaccine and received all doses of it.

Law enforcement investigators reached the conclusion that a U.S. bio-defense researcher who worked for a military laboratory at Fort Detrick conducted the attacks. The researcher, Bruce Ivins, killed himself in 2008 during the investigation. Ivins, however, was never formally charged with a crime, and no direct evidence links him to the attacks. Speculation about his motives centers on Ivins's investment in maintaining national interest in an anthrax vaccine he worked on, and also on his apparent mental instability. In fact, one might argue that these attacks should be considered a bio-crime rather than bio-terror incident, if the motive was not an attempt to influence the conduct of government or to intimidate a civilian population.

Preparation for Biological Attacks

In 2001, before the 9/11 attacks, several U.S. agencies and academic groups conducted a simulated biological attack, codenamed Dark Winter, in which smallpox virus was the weapon. The exercise, which operated on an assumption of about 12 million available doses of smallpox vaccine, based on the then-available stores of smallpox vaccine, "demonstrated serious weaknesses in the public health system that could prevent effective response to bio-terrorism or severe naturally occurring infectious diseases" ("Overview of Potential Agents of Biological Terrorism," Southern Illinois University School of Medicine).

One key weakness exposed in the exercise was a shortage of vaccines; this has since been addressed, at least in the case of smallpox, with the addition of hundreds of millions of doses of smallpox vaccine to U.S. vaccine reserves. Other difficulties exposed were the conflicts between federal and state priorities in managing resources, a shortage of medical infrastructure to deal with mass casualties, and the crucial need for U.S. citizens to trust and cooperate with leaders. The reaction of those exposed to anthrax in the post-9/11 attacks illustrates the challenges embedded in the latter issue: a study published in 2008 suggested that the reticence of many exposed individuals to take the anthrax vaccine reflected their fear of the vaccine's side effects and distrust of medical personnel (Quinn, 2008). In any large-scale bio-terror incident, this distrust may be a major hurdle to effective containment of an infectious agent.

Authorities hope that disaster planning and the devising of effective medical countermeasures for biological attacks will both minimize the impact of such attack, and also act as a deterrent to those who might consider such an attack. If the attack could be easily contained and addressed, then a terrorist or unfriendly nation might have less incentive to initiate one.

Agencies Involved in Bioweapon Response

A variety of U.S. federal, state, and local agencies are involved in public health emergency preparedness and response. The U.S. Congress funds the Centers for Disease Control and Prevention's Office of Public Health Preparedness and Response (PHPR) to build and strengthen national preparedness for public health emergencies caused by natural, accidental, or intentional events. Part of the funding supports the Strategic National Stockpile, which manages stores of vaccines, drugs, and medical supplies that may be deployed in national emergencies. (See below for more on the SNS.)

The U.S. Department of Health and Human Services (HHS) houses several offices involved in public health emergency response. The Office of the Assistant Secretary for Preparedness and Response (ASPR) was created after Hurricane Katrina and is responsible for leadership in prevention, preparation, and response to the adverse health effects of public health emergencies and disasters. ASPR conducts research and builds federal emergency medical operational capabilities. Within ASPR, the Biomedical Advanced Research and Development Authority (BARDA) is responsible for the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies.

The U.S. Department of Homeland Security includes several groups that address bio-weapon threats. The National Biodefense Analysis and Countermeasures Center (NBACC) examines the scientific basis of the risks posed by biological threats. **NBACC's National Biological Threat Characterization Center (NBTCC)** conducts studies and experiments on current and future biological threats, assesses vulnerabilities and conducts risk assessments, and determines potential impacts to guide the development of countermeasures such as detectors, drugs, vaccines, and decontamination technologies. Other offices are responsible for responding to and analyzing bio-weapon attacks after they occur, to help investigators identify perpetrators and determine the origin and method of attack.

State and local health departments, as well as public and private hospitals and local law enforcement agencies, would also be involved in responding to a bio-weapon public health emergency. Their roles are outlined in national response plans and are addressed in detail by organization-specific plans.

Role of the Food and Drug Administration

The U.S. FDA controls the pathway to licensure for vaccines, treatments, diagnostic tests, and other tools for responding to biological threats. The regulatory requirements for licensure of a vaccine are complex and apply to a multi-step process of safety, immunogenicity, and efficacy testing, and post-licensure surveillance. (See the article **Vaccine Development, Testing, and Regulation** to read about this non-emergency approval process.) A typical vaccine might be in development and clinical trials for 10 to 20 years before licensure.

In situations where a new vaccine is needed quickly, the FDA has developed rapid alternative pathways to licensure. One option is an accelerated approval path that could apply in the case of a life-threatening disease with an unlicensed vaccine that has meaningful therapeutic benefit over existing options. Second, in other, more drastic threats, the so-called animal rule may be invoked—if research toward a vaccine or treatment would require exposing humans to a toxic threat, then animal studies, rather than previously conducted studies in humans, may be sufficient for approval. To date, these two rapid pathways have not been invoked for vaccines. More information is available at the FDA's Critical Path Initiative.

U.S. Emergency Use Authorization (EUA) is an option in pandemic and bio-weapon response for both civilian and military populations. After a declaration of emergency by the Department of Health and Human Services secretary, this program allows for use of an unapproved medical product (or a product approved but not for the specific use applicable to the situation at hand) that is the best available treatment or prevention for the threat in question. EUAs were issued for antiviral treatments, a respirator, and a PCR diagnostic test during the 2009 A/H1N1 pandemic.

One challenge to licensing vaccines for response to bio-weapon threats is the absence of some of these disease agents in the natural world. Vaccine efficacy is more difficult to establish when natural exposure to a pathogen is impossible (as with smallpox and other threats) and when human challenge studies are not feasible. The FDA accepts animal testing for proof of efficacy in these cases.

In the fall of 2011, national debate focused on the emergency use of bio-weapon vaccines in children. A simulated anthrax attack code named Dark Zephyr was conducted in February 2011 and raised questions about the use of anthrax vaccine for post-exposure prophylaxis in children. Researchers have never tested the anthrax vaccine for safety and efficacy in children, though it has been extensively studied in adults and given to millions of U.S. servicepeople. After considering the issue in the wake of Dark Zephyr, the National Biodefense Science Board, a federal advisory panel to HHS, decided that testing the vaccine in children is ethically justified, given that it would provide information important to the health and well-being of any child victims of an attack. Critics have disputed that thinking, stating that the possibility of an anthrax attack is too remote to justify exposing children to any risk. HHS has not established a timeline for further action on studying the anthrax vaccine in children.

In the meantime, if a bio-weapon incident involving anthrax occurred, adults would be given three doses of the vaccine, along with oral antibiotics, as post-exposure prophylaxis (PEP) under Emergency Use Authorization, as the vaccine is not currently licensed for PEP nor for use in a three-dose regimen. Children might receive the vaccine under FDA approval of an investigational new drug protocol (IND). Use of anthrax vaccine in children under an IND protocol is not ideal, as it is more suited to clinical trials or an emergency for a single patient.

Vaccine Response to Bioweapon Threats

In a wide-scale emergency in which a vaccine is available or potentially available, a large supply of vaccine would be necessary and needed quickly. Currently, the U.S. Strategic National Stockpile (SNS) has enough smallpox vaccine to vaccinate every person in the country in the event of a bio-weapon attack. The stockpile also holds millions of doses of anthrax vaccine, other vaccines, antiviral medications, and other medical supplies. Quick deployment of a vaccine is essential to its success in preventing disease. For some diseases, vaccinating after exposure may have no effect on preventing disease, and for others, vaccination must occur very quickly after exposure for prophylaxis to work. In the case of smallpox, PEP is likely to be effective when given within four days of exposure to the virus. Plans provide for the smallpox vaccine to be shipped starting on the first day of an attack, and it would continue to be shipped from the stockpile to the rest of the country as needed in the five to six days following the attack.

Bio-security experts have suggested that the use of agents for passive immunization could play a role in response to certain bio-weapon attacks. (Passive immunization is the introduction of antibodies taken from immune donors into nonimmune individuals. The "borrowed" antibodies offer short-lived protection from certain diseases. See our article on **Passive Immunization** for more information.) The advantage of using antibodies rather than vaccines to respond to a bio-terror event is that antibodies provide immediate protection, while a protective response generated by a vaccine is not immediate, and in some cases, may depend on a booster dose given later.

Candidates for this potential application of passive immunization include botulinum toxin, tularemia, anthrax, and plague. For most of these targets, only animal studies have been conducted, so passive immunization in potential bio-weapon events is still in experimental stages.

Conclusion

A biological attack by terrorists or an unfriendly nation is a remote possibility that requires public health emergency response planning. Several multi-agency simulations have exposed weaknesses in systems designed to respond to biological emergencies. These exercises have helped focus planning efforts on the need for emergency plans to address the potential for a large bio-weapons event to overwhelm medical capabilities, cause widespread illness and death, and lead to economic and social disruption. The successful deployment of vaccines, antibodies, and other medications in a bio-weapon event will depend on many factors, such as how many people the attack can harm, the stability of the transportation system in an emergency, the availability of viable vaccines and drugs, and the ability of the public health system to communicate with the public and get the vaccines and medications into the people who need them.

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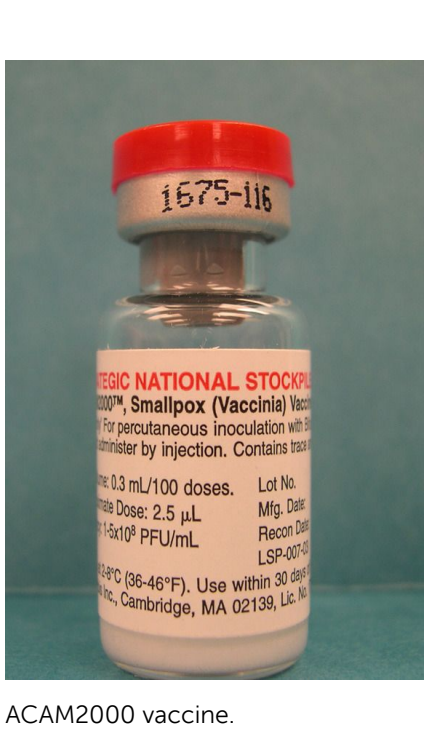
Military smallpox vaccination



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